**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| In re the Application of: | Group Art Unit: Not Yet Assigned |
| **Qun Dang, et al.** | Examiner: Not Yet Assigned |
| Divisional Application of | |
| Serial No.: 09/036,327 | |
| Filed: March 6, 1998 | |
| For: NOVEL PURINE INHIBITORS OF FRUCTOSE-1,6-BISPHOSPHATASE | |

**PRELIMINARY AMENDMENT**

Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination please amend the above-captioned application as follows:

IN THE SPECIFICATION

Kindly amend the specification as follows:

CERTIFICATE OF MAILING
(37 C.F.R. §1.10)

I hereby certify that this paper (along with anything referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as 'Express Mail Post Office To Addressee' in an envelope addressed to the Commissioner for Patents, Washington, D.C. 20231.

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At page 1, line 2 (after the Title of the Invention), please insert:

--Related Applications

This application is a divisional application of U.S. Application Serial No. 09/036,327, filed March 6, 1998, now allowed.- -

At page 4, please replace the paragraph beginning at line 24 with the following paragraph:

Synthetic inhibitors of FBPase have also been reported. Maryanoff reported that fructose-2,6-bisphosphate analogs inhibit FBPase by binding to the substrate site. J. Am. Chem. Soc., 106:7851 (1984); U.S. Patent No. 4,968,790 (1984). These compounds, however, were relatively weak and did not inhibit glucose production in hepatocytes presumably due to poor cell penetration.

At page 6, please replace the paragraph that begins at line 11 with the following paragraph:

FIG. 11B shows the intracellular generation of compound **2.7** in rat hepatocytes treated with compound **16.4**, a prodrug, to inhibit glucose production in rat hepatocytes.

At page 6, please replace the paragraph that begins at line 21 with the following paragraph:

Gruber et al. U.S. patent application Serial Number 08/355,836 , now issued U.S. Patent No. 5,658,889 described the use of inhibitors of the AMP site of FBPase to treat diabetes.

At page 9, lines 9-10, please delete the sentence beginning "The term "alkylsulfonate" . . ."

At page 11, line 2, please replace the first two paragraphs, which begin at lines 1 and 4, with the following two paragraphs:

The term alkoxyalkylaryl refers to the group -alk-O-alk-aryl- wherein each "alk" is independently an alkylene group. "Lower alkoxyalkylaryl" refers to such groups where the alkylene group is lower alkyl.

The term "alkylacylaminoalkyl" refers to the group -alk-N-(COR)-alk- where each alk is an independently selected alkylene group. In "lower alkylacylaminoalkyl" the alkylene groups are lower alkyl.

At page 12, please replace the paragraph that begins at line 1 with the following paragraph:

The term "aminocarboxamidoalkyl" refers to the group -NH-C(O)-N(R)-R wherein each R is an independently selected alkyl group. "Lower aminocarboxamidoalkyl" refers to such groups wherein each R is lower alkyl.

At page 12, please replace the paragraph that begins at line 9 with the following paragraph:

The term "guanidino" refers to both -NR-C(NR)-$NR_2$ as well as -N=$C(NR_2)_2$ where each R group is independently selected from the group of -H, alkyl, alkenyl, alkynyl, aryl, and alicyclic, all optionally substituted.

At page 12, please replace the paragraph that begins at line 12 with the following paragraph:

The term "amidino" refers to -C(NR)-$NR_2$ where each R group is independently selected from the group of -H, alkyl, alkenyl, alkynyl, aryl, and alicyclic, all optionally substituted.

At page 15, please replace the paragraph that begins at line 7 with the following paragraph:

[6] Thio-containing phosphonate ester prodrugs have been described that are useful in the delivery of FBPase inhibitors to hepatocytes. These phosphonate ester prodrugs contain a protected thioethyl moiety as shown in formula E. One or more of the oxygens of the phosphonate can be esterified. Since the mechanism that results in de-esterification requires the generation of a free thiolate, a variety of thiol protecting groups are possible. For example, the

disulfide is reduced by a reductase-mediated process (Puech et al., Antiviral Res., 22: 155-174 (1993)). Thioesters will also generate free thiolates after esterase-mediated hydrolysis. Benzaria, et al., J. Med. Chem., 39:4958 (1996). Cyclic analogs are also possible and were shown to liberate phosphonate in isolated rat hepatocytes. The cyclic disulfide shown below has not been previously described and is novel.

At page 18, please replace the paragraph that begins at line 23 with the following paragraph:

X group nomenclature as used herein in formula 1 describes the group attached to the phosphonate and ends with the group attached to the 6-position of the purine ring. For example, when X is alkylamino, the following structure is intended:

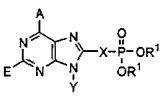
At page 28, please replace the paragraph that begins at line 1 with the following paragraph:

Bis-(4-acetoxyphenyl) esters;

At page 30, please replace the paragraph at line 4 with the following paragraph:

Bis-(bis-2-hydroxyethylamidomethyl) esters.

At page 42, please replace the table that begins on line 1 with the following table:

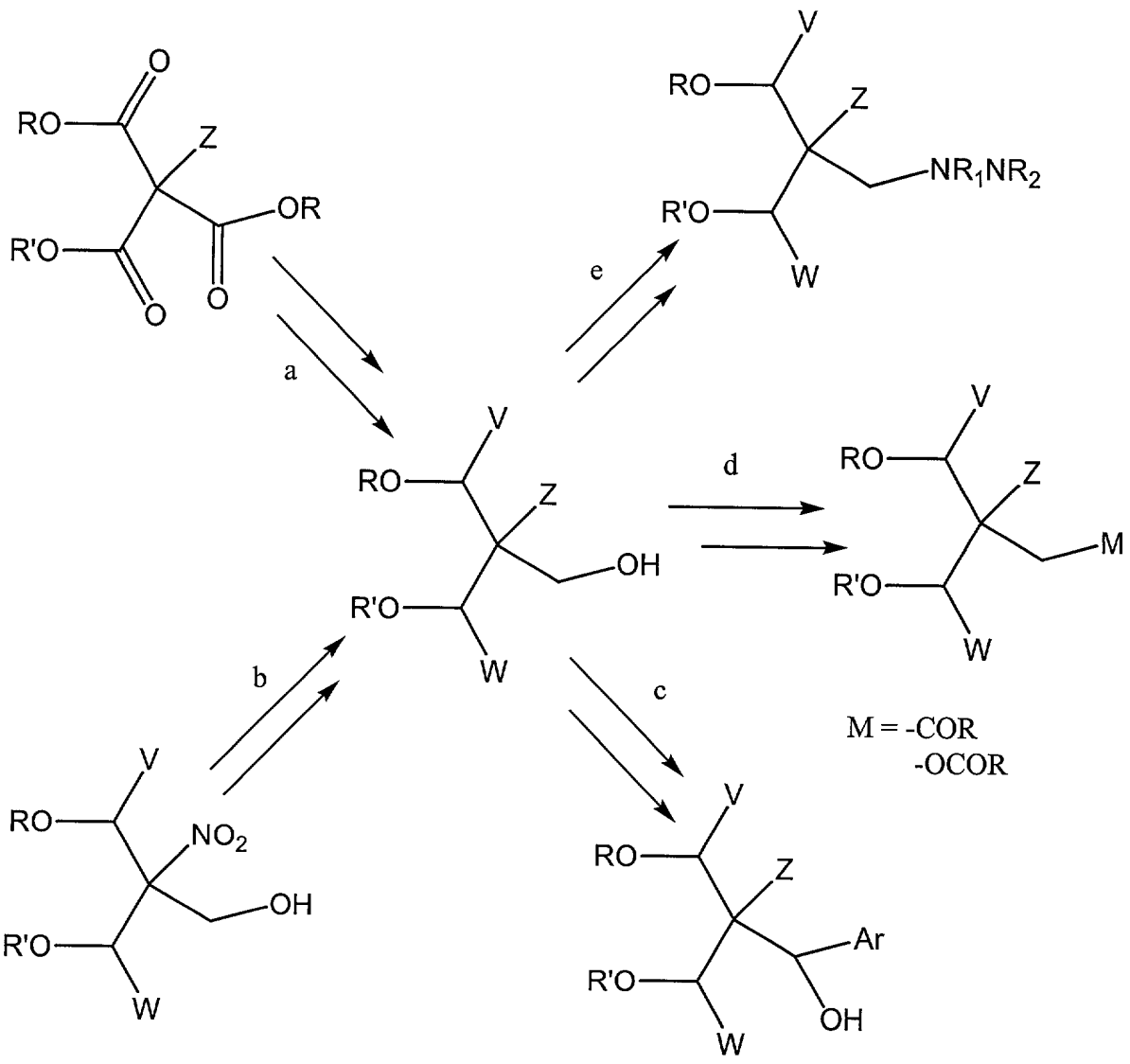
| Table Compound No. | Synthetic Example No. | | |  | |
|---|---|---|---|---|---|
| 269 | | NH2 | F | cyclopropylmethyl | 2,5-furanyl |
| 270 | | NH2 | Cl | cyclopropylmethyl | 2,5-furanyl |
| 271 | | NH2 | Br | cyclopropylmethyl | 2,5-furanyl |
| 272 | | NH2 | Et | cyclopropylmethyl | 2,5-furanyl |
| 273 | | NH2 | CN | cyclopropylmethyl | 2,5-furanyl |
| 274 | | NH2 | Me | cyclopropylmethyl | CONHCH2 |
| 275 | | NH2 | SMe | cyclopropylmethyl | CONHCH2 |

| | | | | | |
|---|---|---|---|---|---|
| 276 | | NH2 | F | cyclopropylmethyl | CONHCH2 |
| 277 | | NH2 | Cl | cyclopropylmethyl | CONHCH2 |
| 278 | | NH2 | Br | cyclopropylmethyl | CONHCH2 |
| 279 | | NH2 | Et | cyclopropylmethyl | CONHCH2 |
| 280 | | NH2 | CN | cyclopropylmethyl | CONHCH2 |
| 281 | | NH2 | Me | cyclopropylmethyl | NHCOCH2 |
| 282 | | NH2 | SMe | cyclopropylmethyl | NHCOCH2 |
| 283 | | NH2 | F | cyclopropylmethyl | NHCOCH2 |
| 284 | | NH2 | Cl | cyclopropylmethyl | NHCOCH2 |
| 285 | | NH2 | Br | cyclopropylmethyl | NHCOCH2 |
| 286 | | NH2 | Et | cyclopropylmethyl | NHCOCH2 |
| 287 | | NH2 | CN | cyclopropylmethyl | NHCOCH2 |
| 288 | 2.18 | NH2 | H | 3-(1-imidazolylpropyl) | 2,5-furanyl |
| 289 | 19.1 | NH2 | H | neopentyl | 1,2-C6H4-O- |
| 290 | 21.1 | NH2 | H | 2-phenethyl | CONHCH2 |

At page 45, please replace the paragraph that begins at line 23 with the following paragraph:

Such reactive dichlorophosphonate intermediates can be prepared from the corresponding phosphonic acids and the chlorinating agents e.g. thionyl chloride (Starrett, et al, *J. Med. Chem.*, **1994**, 1857), oxalyl chloride (Stowell, et al, *Tetrahedron Lett.*, **1990**, *31*: 3261), and phosphorus pentachloride (Quast, et al, *Synthesis*, **1974**, 490). Alternatively, these dichlorophosphonates can also be generated from disilyl phosphonate esters (Bhongle, et al, *Synth. Commun.*, **1987**, *17*: 1071) and dialkyl phosphonate esters (Still, et al, *Tetrahedron Lett.*, **1983**, *24*: 4405; Patois, et al, *Bull. Soc. Chim. Fr.*, **1993**, *130*: 485).

At page 49, please replace the reaction scheme that appears immediately after line 2 with the following reaction scheme:




At page 68, please replace the paragraph that begins at line 10 with the following paragraph:

Step A. A mixture of $N^9$-phenethyl-8-bromoadenine (1 mmol), tetrakis (triphenylphosphine)palladium (0.05 mmol), and triethylamine (5 mmol) in DMF in a sealed tube was warmed at 110 °C under 50 psi of carbon monoxide. After 24 h the cooled reaction mixture was evaporated and purified through chromatography to give $N^9$-phenethyl-8-methoxycarbonyladenine as a yellow solid. TLC: Rf= 0.12, 5 % MeOH-$CH_2Cl_2$.

At page 81, please replace the paragraph that begins at line 10 with the following paragraph:

Step A. A solution of 2-amino-4,6-dichloropyrimidine (1 mmol), neopentylamine (1.05 mmol), and triethylamine (2 mmol) in n-butanol was stirred at 110 °C for 12 h. Extraction and chromatography gave 2-amino-4-chloro-6-neopentylpyrimidine as a yellow solid. TLC: $R_f = 0.2$, 30 % EtOAc-hexane.

At page 83, please replace the paragraph that begins at line 27 with the following paragraph:

Following the above described procedures, other cyclic esters are also prepared, such as $N^9$-neopentyl-8-(2-(5-(2-(methoxycarbonyloxymethyl)-propan-1,3 -yl)phosphono)furanyl)adenine, $N^9$-neopentyl-8-(2-(5-(2-(hydroxymethyl)-propan-1,3 -yl)phosphono)furanyl)adenine, $N^9$-neopentyl-8-(2-(5-(2,2-dihydroxymethylpropan-1,3 -yl)phosphono)furanyl)adenine, $N^9$-neopentyl-8-(2-(5-(2-(methoxycarbonyloxymethyl)propan-1,3 -yl)phosphono)-furanyl)adenine is prepared by coupling $N^9$-neopentyl-8-(2-(5-phosphono)-furanyl)adenine with 2-(methoxycarbonyloxymethyl)-1,3-propanediol which was prepared as follows:

At page 85, please replace the paragraph that begins at line 9 with the following paragraph:

A mixture of $N^9$-neopentyl-8-(2-(5-phosphono)furanyl)adenine (1 mmol) and tris(hydroxymethyl)aminomethane (1.05 mmol) in methanol is stirred at 25 °C for 24 h. Evaporation gives $N^9$-neopentyl-8-(2-(5-phosphono)furanyl)adenine tris(hydroxymethyl)aminomethane salt.

At page 85, please replace the paragraph that begins at line 13 with the following paragraph:

Examples of the methods of the present invention include the following. It will be understood that these examples are exemplary and that the method of the invention is not limited solely to these examples.

At page 85, please replace the paragraph that begins at line 21 with the following paragraph:

i. Animals with pancreatic b-cells destroyed by specific chemical cytotoxins such as Alloxan or Streptozotocin (e.g. the Streptozotocin-treated mouse, -rat, dog, and -monkey). Kodama, H., Fujita, M., Yamaguchi, I., *Japanese Journal of Pharmacology* **1994**, *66*, 331-336 (mouse); Youn, J.H., Kim, J.K., Buchanan, T.A., *Diabetes* **1994**, *43*, 564-571 (rat); Le Marchand, Y., Loten, E.G., Assimacopoulos-Jannet, F., et al., *Diabetes* **1978**, *27*, 1182-88 (dog); and Pitkin, R.M., Reynolds, W.A., *Diabetes* **1970**, *19*, 70-85 (monkey).

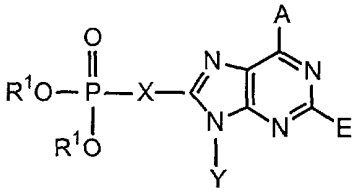
At page 91, please replace the paragraph beginning on line 24 with the following paragraph:

*Phosphofructokinase*: Enzyme (rabbit liver) was purchased from Sigma. Activity was measured at 30 °C in reactions in which the formation of fructose 1,6-bisphosphate was coupled to the oxidation of NADH via the action of aldolase, triosephosphate isomerase, and α-glycerophosphate dehydrogenase. Reaction mixtures (200 µl) were made up in 96-well microtitre plates and were read at 340 nm in a Molecular Devices Microplate Reader. The mixtures consisted of 200 mM Tris-HCl pH 7.0, 2 mM DTT, 2 mM $MgCl_2$, 0.2 mM NADH, 0.2 mM ATP, 0.5 mM Fructose 6-phosphate, 1 unit aldolase/mL, 3 units/mL triosephosphate isomerase, and 4 units/mL α-glycerophosphate dehydrogenase. Test compound concentrations ranged from 1 to 500 µM. Reactions were started by the addition of 0.0025 units of phosphofructokinase and were monitored for 15 minutes.

IN THE CLAIMS

Please cancel claims 2-33, 40 and 43 without prejudice. Please amend claims 1, 34-37, 39 and 42 as follows:

1. (Amended) A compound of formula 1:



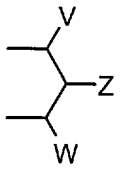
wherein

A is selected from the group consisting of $-NR^8_2$, $-NHSO_2R^3$, $-OR^5$, $-SR^5$, halo, lower alkyl, $-CON(R^4)_2$, guanidino, amidino, -H, and perhaloalkyl;

E is selected from the group consisting of -H, halo, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^7_2$;

X together with Y forms a cyclic group selected from the group of cyclic alkyl, heterocyclic, and aryl;

$R^1$ is independently selected from the group consisting of -H, alkyl, aryl, heteroalicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, –alk-aryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2$-C(O)-$R^3$, $-C(R^2)_2$-OC (O)$R^3$, $-C(R^2)_2$-O-C(O)O$R^3$, $-C(R^2)_2OC(O)SR^3$, –alk-S-C(O)$R^3$, –alk-S-S-alkylhydroxy, and –alk-S-S-S-alkylhydroxy, or together $R^1$ and $R^1$ are –alk-S-S-alk- to form a cyclic group, wherein each "alk" is an independently selected alkylene, or together $R^1$ and $R^1$ are




wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected via a chain of 3-5 atoms, only one of which can be a heteroatom, to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected via a chain of 3 carbon atoms to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2_2$, $-CH_2Ar$, -CH(Ar)OH, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

$R^2$ is selected from the group consisting of $R^3$ and -H;

$R^3$ is selected from the group consisting of alkyl, aryl, alicyclic, heteroalicyclic, and aralkyl;

$R^4$ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, and lower aryl;

$R^5$ is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, lower heteroalicyclic, and lower alicyclic;

$R^6$ is independently selected from the group consisting of -H, and lower alkyl;

$R^7$ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

$R^8$ is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together said $R^8$ groups form a bidendate alkylene;

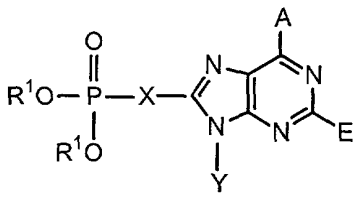
$R^9$ is selected from the group consisting of alkyl, aralkyl, , heteroalicyclic, and alicyclic;

$R^{10}$ is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

$R^{11}$ is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.

34. (Amended) A method of treating an animal for diabetes mellitus, comprising administering to said animal a therapeutically effective amount of a compound of formula (1):



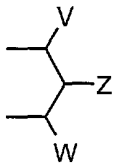

wherein

A is selected from the group consisting of $-NR^8_2$, $-NHSO_2R^3$, $-OR^5$, $-SR^5$, halo, lower alkyl, $-CON(R^4)_2$, guanidino, amidino, -H, and perhaloalkyl;

E is selected from the group consisting of -H, halo, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^7_2$;

X together with Y forms a cyclic group selected from the group of cyclic alkyl, heterocyclic, and aryl;

$R^1$ is independently selected from the group consisting of -H, alkyl, aryl, heteroalicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, –alk-aryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2$-C(O)-$R^3$, $-C(R^2)_2$-OC (O)$R^3$, $-C(R^2)_2$-O-C(O)$OR^3$, $-C(R^2)_2OC(O)SR^3$, –alk-S-C(O)$R^3$, –alk-S-S-alkylhydroxy, and –alk-S-S-S-alkylhydroxy, or together $R^1$ and $R^1$ are –alk-S-S-alk- to form a cyclic group, wherein each "alk" is an independently selected alkylene, or together $R^1$ and $R^1$ are




wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected via a chain of 3-5 atoms, only one of which can be a heteroatom, to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected via a chain of 3 carbon atoms to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2_2$, $-CH_2Ar$, -CH(Ar)OH, $-CH(CH=CR^2R^2)OH$, $-CH(C\equiv CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

$R^2$ is selected from the group consisting of $R^3$ and -H;

$R^3$ is selected from the group consisting of alkyl, aryl, alicyclic, heteroalicyclic, and aralkyl;

$R^4$ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, and lower aryl;

$R^5$ is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, lower heteroalicyclic, and lower alicyclic;

$R^6$ is independently selected from the group consisting of -H, and lower alkyl;

$R^7$ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

$R^8$ is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together said $R^8$ groups form a bidendate alkylene;

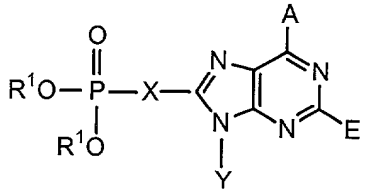
$R^9$ is selected from the group consisting of alkyl, aralkyl, , heteroalicyclic, and alicyclic;

$R^{10}$ is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

$R^{11}$ is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.

35. (Amended) A method of lowering blood glucose levels in an animal in need thereof, comprising administering to said animal a pharmaceutically acceptable amount of a compound of formula (1):



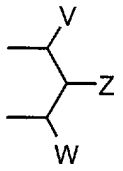

wherein

A is selected from the group consisting of $-NR^8_2$, $-NHSO_2R^3$, $-OR^5$, $-SR^5$, halo, lower alkyl, $-CON(R^4)_2$, guanidino, amidino, -H, and perhaloalkyl;

E is selected from the group consisting of -H, halo, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^7_2$;

X together with Y forms a cyclic group selected from the group of cyclic alkyl, heterocyclic, and aryl;

$R^1$ is independently selected from the group consisting of -H, alkyl, aryl, heteroalicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, –alk-aryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2$-C(O)-$R^3$, $-C(R^2)_2$-OC (O)$R^3$, $-C(R^2)_2$-O-C(O)O$R^3$, $-C(R^2)_2OC(O)SR^3$, –alk-S-C(O)$R^3$, –alk-S-S-alkylhydroxy, and –alk-S-S-S-alkylhydroxy, or together $R^1$ and $R^1$ are –alk-S-S-alk- to form a cyclic group, wherein each "alk" is an independently selected alkylene, or together $R^1$ and $R^1$ are




wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected via a chain of 3-5 atoms, only one of which can be a heteroatom, to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected via a chain of 3 carbon atoms to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2_2$, $-CH_2Ar$, -CH(Ar)OH, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

$R^2$ is selected from the group consisting of $R^3$ and -H;

$R^3$ is selected from the group consisting of alkyl, aryl, alicyclic, heteroalicyclic, and aralkyl;

$R^4$ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, and lower aryl;

$R^5$ is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, lower heteroalicyclic, and lower alicyclic;

$R^6$ is independently selected from the group consisting of -H, and lower alkyl;

$R^7$ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

$R^8$ is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together said $R^8$ groups form a bidendate alkylene;

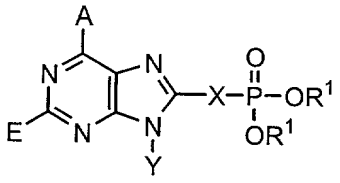
$R^9$ is selected from the group consisting of alkyl, aralkyl, , heteroalicyclic, and alicyclic;

$R^{10}$ is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

$R^{11}$ is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.

36. (Amended) A method of inhibiting FBPase at the AMP site in patients in need thereof, comprising administering to said patients an FBPase inhibitory amount of a compound of formula (1):



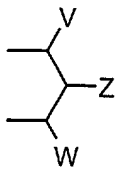

wherein

A is selected from the group consisting of $-NR^8_2$, $-NHSO_2R^3$, $-OR^5$, $-SR^5$, halo, lower alkyl, $-CON(R^4)_2$, guanidino, amidino, -H, and perhaloalkyl;

E is selected from the group consisting of -H, halo, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^7_2$;

X together with Y forms a cyclic group selected from the group of cyclic alkyl, heterocyclic, and aryl;

$R^1$ is independently selected from the group consisting of -H, alkyl, aryl, heteroalicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, –alk-aryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2$-C(O)-$R^3$, $-C(R^2)_2$-OC (O)$R^3$, $-C(R^2)_2$-O-C(O)O$R^3$, $-C(R^2)_2OC(O)SR^3$, –alk-S-C(O)$R^3$, –alk-S-S-alkylhydroxy, and –alk-S-S-S-alkylhydroxy, or together $R^1$ and $R^1$ are –alk-S-S-alk- to form a cyclic group, wherein each "alk" is an independently selected alkylene, or together $R^1$ and $R^1$ are




wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected via a chain of 3-5 atoms, only one of which can be a heteroatom, to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected via a chain of 3 carbon atoms to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2_2$, $-CH_2Ar$, -CH(Ar)OH, $-CH(CH=CR^2R^2)OH$, $-CH(C\equiv CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

$R^2$ is selected from the group consisting of $R^3$ and -H;

$R^3$ is selected from the group consisting of alkyl, aryl, alicyclic, heteroalicyclic, and aralkyl;

$R^4$ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, and lower aryl;

$R^5$ is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, lower heteroalicyclic, and lower alicyclic;

$R^6$ is independently selected from the group consisting of -H, and lower alkyl;

$R^7$ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

$R^8$ is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together said $R^8$ groups form a bidendate alkylene;

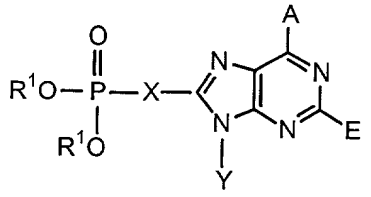
$R^9$ is selected from the group consisting of alkyl, aralkyl, , heteroalicyclic, and alicyclic;

$R^{10}$ is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

$R^{11}$ is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.

37. (Amended) A method of inhibiting gluconeogenesis in animal in need thereof, comprising administering to said animal an effective amount of a compound of formula (1):



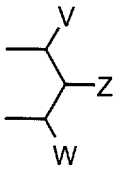

wherein

A is selected from the group consisting of $-NR^8_2$, $-NHSO_2R^3$, $-OR^5$, $-SR^5$, halo, lower alkyl, $-CON(R^4)_2$, guanidino, amidino, -H, and perhaloalkyl;

E is selected from the group consisting of -H, halo, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^7_2$;

X together with Y forms a cyclic group selected from the group of cyclic alkyl, heterocyclic, and aryl;

$R^1$ is independently selected from the group consisting of -H, alkyl, aryl, heteroalicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, –alk-aryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $-C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, $-alk-S-C(O)R^3$, –alk-S-S-alkylhydroxy, and –alk-S-S-S-alkylhydroxy, or together $R^1$ and $R^1$ are –alk-S-S-alk- to form a cyclic group, wherein each "alk" is an independently selected alkylene, or together $R^1$ and $R^1$ are




wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected via a chain of 3-5 atoms, only one of which can be a heteroatom, to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected via a chain of 3 carbon atoms to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2_2$, $-CH_2Ar$, -CH(Ar)OH, $-CH(CH=CR^2R^2)OH$, $-CH(C\equiv CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

$R^2$ is selected from the group consisting of $R^3$ and -H;

$R^3$ is selected from the group consisting of alkyl, aryl, alicyclic, heteroalicyclic, and aralkyl;

$R^4$ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, and lower aryl;

$R^5$ is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, lower heteroalicyclic, and lower alicyclic;

$R^6$ is independently selected from the group consisting of -H, and lower alkyl;

$R^7$ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

$R^8$ is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together said $R^8$ groups form a bidendate alkylene;

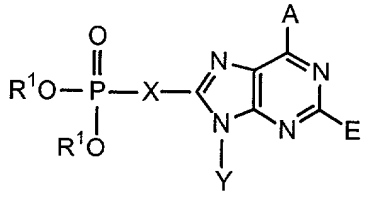
$R^9$ is selected from the group consisting of alkyl, aralkyl, , heteroalicyclic, and alicyclic;

$R^{10}$ is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

$R^{11}$ is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.

39. (Amended) A method of treating an animal for a disease derived from abnormally elevated insulin levels, comprising administering to said animal a therapeutically effective amount of a fructose-1,6-bisphosphatase inhibitor wherein said inhibitor is a compound of formula (1):



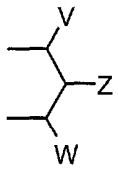
wherein

A is selected from the group consisting of $-NR^8{}_2$, $-NHSO_2R^3$, $-OR^5$, $-SR^5$, halo, lower alkyl, $-CON(R^4)_2$, guanidino, amidino, -H, and perhaloalkyl;

E is selected from the group consisting of -H, halo, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^7{}_2$;

X together with Y forms a cyclic group selected from the group of cyclic alkyl, heterocyclic, and aryl;

$R^1$ is independently selected from the group consisting of -H, alkyl, aryl, heteroalicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, –alk-aryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2$-C(O)-$R^3$, $-C(R^2)_2$-OC (O)$R^3$, $-C(R^2)_2$-O-C(O)$OR^3$, $-C(R^2)_2OC(O)SR^3$, –alk-S-C(O)$R^3$, –alk-S-S-alkylhydroxy, and –alk-S-S-S-alkylhydroxy, or together $R^1$ and $R^1$ are –alk-S-S-alk- to form a cyclic group, wherein each "alk" is an independently selected alkylene, or together $R^1$ and $R^1$ are




wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected via a chain of 3-5 atoms, only one of which can be a heteroatom, to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected via a chain of 3 carbon atoms to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2_2$, $-CH_2Ar$, -CH(Ar)OH, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

$R^2$ is selected from the group consisting of $R^3$ and -H;

$R^3$ is selected from the group consisting of alkyl, aryl, alicyclic, heteroalicyclic, and aralkyl;

$R^4$ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, and lower aryl;

$R^5$ is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, lower heteroalicyclic, and lower alicyclic;

$R^6$ is independently selected from the group consisting of -H, and lower alkyl;

$R^7$ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

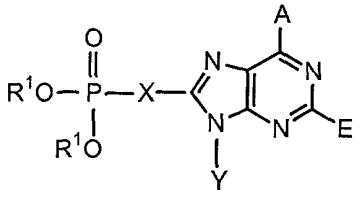
$R^8$ is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together said $R^8$ groups form a bidendate alkylene;

$R^9$ is selected from the group consisting of alkyl, aralkyl, , heteroalicyclic, and alicyclic;

$R^{10}$ is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

$R^{11}$ is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and pharmaceutically acceptable prodrugs and salts thereof.

42. (Amended) A method of treating an animal with excess glycogen storage disease, comprising administering to said animal in need thereof a therapeutically effective amount of a fructose-1,6-bisphosphatase inhibitor, wherein said inhibitor is a compound of formula (1):



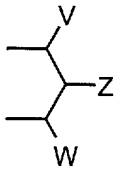

wherein

A is selected from the group consisting of $-NR^8_2$, $-NHSO_2R^3$, $-OR^5$, $-SR^5$, halo, lower alkyl, $-CON(R^4)_2$, guanidino, amidino, -H, and perhaloalkyl;

E is selected from the group consisting of -H, halo, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^7_2$;

X together with Y forms a cyclic group selected from the group of cyclic alkyl, heterocyclic, and aryl;

$R^1$ is independently selected from the group consisting of -H, alkyl, aryl, heteroalicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, –alk-aryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2$-OC (O)$R^3$, $-C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, –alk-S-C(O)$R^3$, –alk-S-S-alkylhydroxy, and –alk-S-S-S-alkylhydroxy, or together $R^1$ and $R^1$ are –alk-S-S-alk- to form a cyclic group, wherein each "alk" is an independently selected alkylene, or together $R^1$ and $R^1$ are




wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected via a chain of 3-5 atoms, only one of which can be a heteroatom, to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected via a chain of 3 carbon atoms to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2_2$, $-CH_2Ar$, -CH(Ar)OH, $-CH(CH=CR^2R^2)OH$, $-CH(C\equiv CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

$R^2$ is selected from the group consisting of $R^3$ and -H;

$R^3$ is selected from the group consisting of alkyl, aryl, alicyclic, heteroalicyclic, and aralkyl;

$R^4$ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, and lower aryl;

$R^5$ is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, lower heteroalicyclic, and lower alicyclic;

$R^6$ is independently selected from the group consisting of -H, and lower alkyl;

$R^7$ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

$R^8$ is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together said $R^8$ groups form a bidendate alkylene;

$R^9$ is selected from the group consisting of alkyl, aralkyl, , heteroalicyclic, and alicyclic;

$R^{10}$ is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

$R^{11}$ is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.

## REMARKS

Upon entry of this amendment, claims 1, 34-39 and 41-42 are pending in the application. Claims 1, 34-37, 39, and 42 have been amended, while claim 2-33, 40 and 43 have been canceled. The specification and the specified claims have been amended to conform with amendments to parent Application Serial No. 09/036,327, now allowed. The amendments to the specification and the claims submitted herewith are fully supported by the application as filed. Therefore no new matter has been added by these amendments.

Claims 1, 34-37, 39, and 42 have been amended to eliminate the Group I compounds that were elected in parent Application Serial No. 09/036,327 following a restriction requirement. As amended, claims 1, 34-37, 39, and 42 are directed towards the invention of Group II which was non-elected in the parent application. In addition, claims 1, 34-37, 39 and 42 have been amended so as to conform with the corresponding allowed claims in the parent application. These latter amendments have been made only for the purpose of more clearly defining the invention and do not narrow the scope of any one of claims 1, 34-37, 39 and 42 within the meaning of *Festo*.

## Conclusion

In view of the foregoing remarks and amendments, it is believed that the entire application is in condition for allowance, and such action is respectfully requested at the Examiner's earliest convenience. If there are any questions concerning this communication, the Examiner is invited to call the undersigned at the telephone number provided below.

The Commissioner is hereby authorized to charge any additional fees which may be required, or to credit any overpayment, to **Deposit Account No. 50-1273**.

Respectfully Submitted,

BROBECK, PHLEGER & HARRISON LLP

August 30, 2001

By: Richard Pagliery
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## VERSION WITH MARKINGS TO SHOW CHANGES

The specification has been amended as follows:

At page 1, line 2 (after the Title of the Invention), the following was inserted:

--Related Applications

This application is a divisional application of U.S. Application Serial No. 09/036,327, filed March 6, 1998, now allowed.- -

At page 4, the paragraph beginning at line 24 was replaced with the following paragraph with the noted changes:

Synthetic inhibitors of FBPase have also been reported. [McNiel] Maryanoff reported that fructose-2,6-bisphosphate analogs inhibit FBPase by binding to the substrate site. [J. Med. Chem.] J. Am. Chem. Soc., 106:7851 (1984); U.S. Patent No. 4,968,790 (1984). These compounds, however, were relatively weak and did not inhibit glucose production in hepatocytes presumably due to poor cell penetration.

At page 6, the paragraph that begins at line 11 was replaced with the following paragraph with the noted changes:

FIG. 11B shows the intracellular generation of compound **2.7** in rat hepatocytes treated with [compound 16.4] compound **16.4**, a prodrug, to inhibit glucose production in rat hepatocytes.

At page 6, the paragraph that begins at line 21 was replaced with the following paragraph with the noted changes:

Gruber et al. U.S. patent application Serial Number 08/355,836 [allowed] , now issued U.S. Patent No. 5,658,889 described the use of inhibitors of the AMP site of FBPase to treat diabetes.

At page 9, lines 9-10, the sentence beginning "The term "alkylsulfonate" . . ." was deleted.

At page 11, line 2, the first two paragraphs, which begin at lines 1 and 4, were replaced with the following two paragraphs with the noted changes:

The term ["aloxyalkylaryl"] alkoxyalkylaryl refers to the group -alk-O-alk-aryl- wherein each "alk" is independently an alkylene group. "Lower alkoxyalkylaryl" refers to such groups where the alkylene group is lower alkyl.

The term ["alkylacylaminoalkyl] "alkylacylaminoalkyl" refers to the group -alk-N-(COR)-alk- where each alk is an independently selected alkylene group. In "lower alkylacylaminoalkyl" the alkylene groups are lower alkyl.

At page 12, the paragraph that begins at line 1 was replaced with the following paragraph with the noted changes:

The term ["aminocaboxamidoalkyl"] "aminocarboxamidoalkyl" refers to the group -NH-C(O)-N(R)-R wherein each R is an independently selected alkyl group. "Lower aminocarboxamidoalkyl" refers to such groups wherein each R is lower alkyl.

At page 12, the paragraph that begins at line 9 was replaced with the following paragraph with the noted changes:

The term ["guanidine"] "guanidino" refers to both -NR-C(NR)-$NR_2$ as well as -N=C($NR_2$)$_2$ where each R group is independently selected from the group of -H, alkyl, alkenyl, alkynyl, aryl, and alicyclic, all optionally substituted.

At page 12, the paragraph that begins at line 12 was replaced with the following paragraph with the noted changes:

The term ["amidine"] "amidino" refers to -C(NR)-$NR_2$ where each R group is independently selected from the group of -H, alkyl, alkenyl, alkynyl, aryl, and alicyclic, all optionally substituted.

At page 15, the paragraph that begins at line 7 was replaced with the following paragraph with the noted changes:

[6] Thio-containing phosphonate [phosphonate] ester prodrugs have been described that are useful in the delivery of FBPase inhibitors to hepatocytes. These phosphonate ester prodrugs contain a protected thioethyl moiety as shown in formula E. One or more of the oxygens of the phosphonate can be esterified. Since the mechanism that results in de-esterification requires the generation of a free thiolate, a variety of thiol protecting groups are possible. For example, the disulfide is reduced by a reductase-mediated process (Puech et al., Antiviral Res., 22: 155-174 (1993)). Thioesters will also generate free thiolates after esterase-mediated hydrolysis. Benzaria, et al., J. Med. Chem., 39:4958 (1996). Cyclic analogs are also possible and were shown to liberate phosphonate in isolated rat hepatocytes. The cyclic disulfide shown below has not been previously described and is novel.

At page 18, the paragraph that begins at line 23 was replaced with the following paragraph with the noted changes:

X group nomenclature as used herein in formula 1 describes the group attached to the phosphonate and ends with the group attached to the [2-position of the benzimidazole ring] 6-position of the purine ring. For example, when X is alkylamino, the following structure is intended:

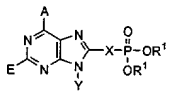
At page 28, the paragraph that begins at line 1 was replaced with the following paragraph with the noted changes:

[Bis-(4-aceyloxyphenyl) esters;] Bis-(4-acetoxyphenyl) esters;

At page 30, the paragraph that begins at line 4 was replaced with the following paragraph with the noted changes:

[Bis-(bis-2-hydroxyethylamidomthyl) esters.] Bis-(bis-2-hydroxyethylamidomethyl) esters.

At page 42, the table that begins on line 1 was replaced with the following table with the noted changes:

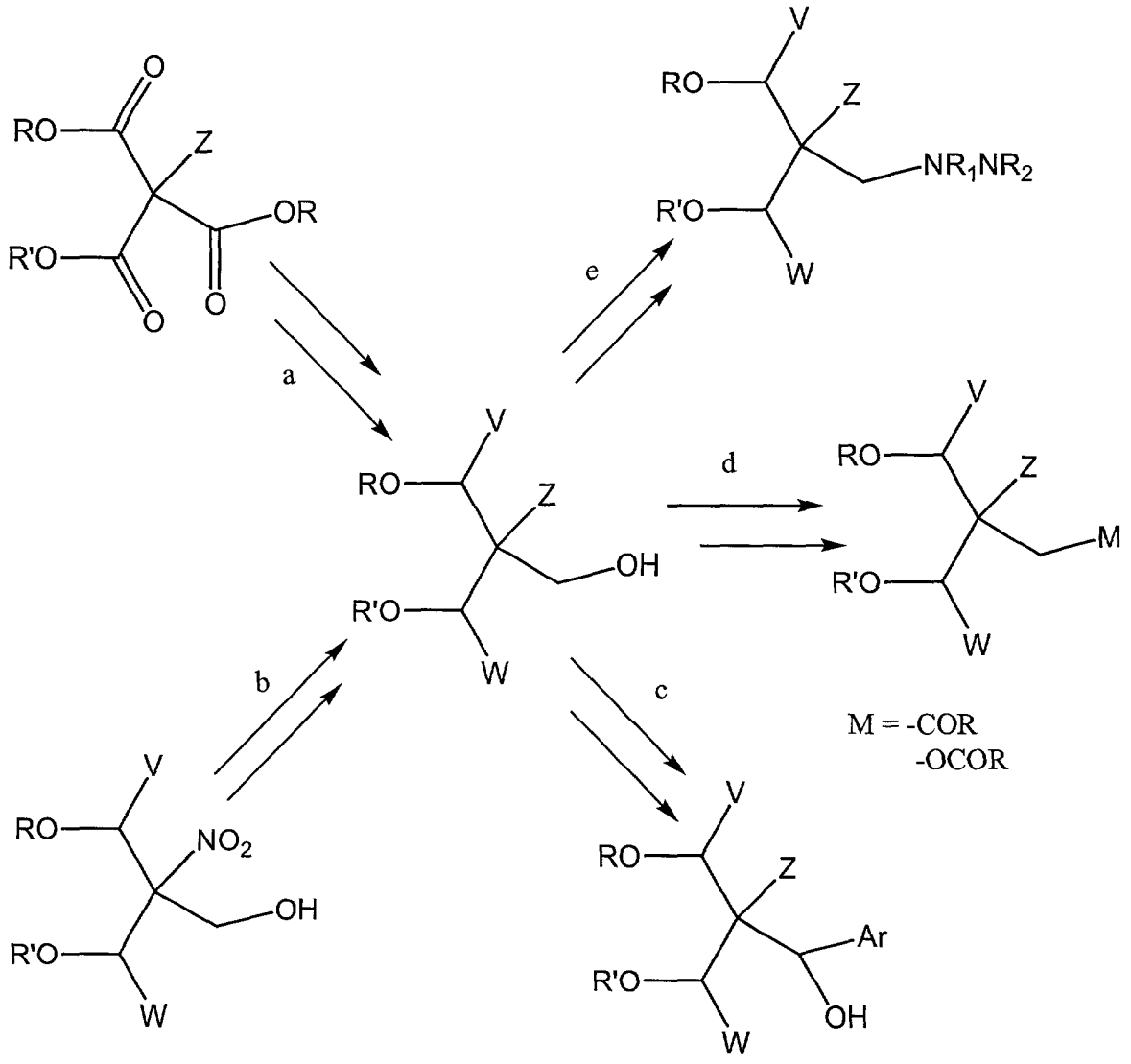
| Table Compound No. | Synthetic Example No. | | |  | |
|---|---|---|---|---|---|
| 269 | | NH2 | F | cyclopropylmethyl | 2,5-furanyl |
| 270 | | NH2 | Cl | [cycloproprylmethyl] cyclopropylmethyl | 2,5-furanyl |
| 271 | | NH2 | Br | cyclopropylmethyl | 2,5-furanyl |
| 272 | | NH2 | Et | cyclopropylmethyl | 2,5-furanyl |
| 273 | | NH2 | CN | cyclopropylmethyl | 2,5-furanyl |
| 274 | | NH2 | Me | cyclopropylmethyl | CONHCH2 |
| 275 | | NH2 | SMe | cyclopropylmethyl | CONHCH2 |
| 276 | | NH2 | F | cyclopropylmethyl | CONHCH2 |
| 277 | | NH2 | Cl | [cycloproprylmethyl] cyclopropylmethyl | CONHCH2 |
| 278 | | NH2 | Br | cyclopropylmethyl | CONHCH2 |
| 279 | | NH2 | Et | cyclopropylmethyl | CONHCH2 |
| 280 | | NH2 | CN | cyclopropylmethyl | CONHCH2 |
| 281 | | NH2 | Me | cyclopropylmethyl | NHCOCH2 |
| 282 | | NH2 | SMe | cyclopropylmethyl | NHCOCH2 |
| 283 | | NH2 | F | cyclopropylmethyl | NHCOCH2 |

| | | | | | |
|---|---|---|---|---|---|
| 284 | | NH2 | Cl | [cycloproprylmeth yl] cyclopropylmethyl | NHCOCH2 |
| 285 | | NH2 | Br | cyclopropylmethyl | NHCOCH2 |
| 286 | | NH2 | Et | cyclopropylmethyl | NHCOCH2 |
| 287 | | NH2 | CN | cyclopropylmethyl | NHCOCH2 |
| 288 | 2.18 | NH2 | H | 3-(1-imidazolylpropyl) | 2,5-furanyl |
| 289 | 19.1 | NH2 | H | neopentyl | 1,2-C6H4-O- |
| 290 | 21.1 | NH2 | H | 2-phenethyl | CONHCH2 |

At page 45, the paragraph that begins at line 23 was replaced with the following paragraph with the noted changes:

Such reactive dichlorophosphonate intermediates[,] can be prepared from the corresponding phosphonic acids and the chlorinating agents e.g. thionyl chloride (Starrett, et al, *J. Med. Chem.*, **1994**, 1857), oxalyl chloride (Stowell, et al, *Tetrahedron Lett.*, **1990**, *31*: 3261), and phosphorus pentachloride (Quast, et al, *Synthesis*, **1974**, 490). Alternatively, these dichlorophosphonates can also be generated from disilyl phosphonate esters (Bhongle, et al, *Synth. Commun.*, **1987**, *17*: 1071) and dialkyl phosphonate esters (Still, et al, *Tetrahedron Lett.*, **1983**, *24*: 4405; Patois, et al, *Bull. Soc. Chim. Fr.*, **1993**, *130*: 485).

At page 49, the reaction scheme that appears immediately after line 2 was deleted and replaced with the following reaction scheme:




At page 68 the paragraph that begins at line 10 was replaced with the following paragraph with the noted changes:

Step A. A mixture of $N^9$-phenethyl-8-bromoadenine (1 mmol), tetrakis (triphenylphosphine)palladium (0.05 mmol), and triethylamine (5 mmol) in DMF in a sealed tube was warmed at 110 °C under 50 psi of carbon monoxide. After 24 h the cooled reaction

mixture was evaporated and purified through chromatography to [gave] give $N^9$-phenethyl-8-methoxycarbonyladenine as a yellow solid. TLC: Rf= 0.12, 5 % MeOH-$CH_2Cl_2$.

At page 81, the paragraph that begins at line 10 was replaced with the following paragraph with the noted changes:

Step A. A solution of [2-amino-4,6-dichloropyrmidine] 2-amino-4,6-dichloropyrimidine (1 mmol), neopentylamine (1.05 mmol), and triethylamine (2 mmol) in n-butanol was stirred at 110 °C for 12 h. Extraction and chromatography gave 2-amino-4-chloro-6-neopentylpyrimidine as a yellow solid. TLC: $R_f$ = 0.2, 30 % EtOAc-hexane.

At page 83, the paragraph that begins at line 27 was replaced with the following paragraph with the noted changes:

Following the above described procedures, other cyclic esters are also prepared, such as $N^9$-neopentyl-8-(2-(5-(2-(methoxycarbonyloxymethyl)-propan-1,3 -yl)phosphono)furanyl)adenine, $N^9$-neopentyl-8-(2-(5-(2-(hydroxymethyl)-propan-1,3 -yl)phosphono)furanyl)adenine, $N^9$-neopentyl-8-(2-(5-(2,2-dihydroxymethylpropan-1,3 -yl)phosphono)furanyl)adenine[.], $N^9$-neopentyl-8-(2-(5-(2-(methoxycarbonyloxymethyl)propan-1,3 -yl)phosphono)-furanyl)adenine is prepared by coupling $N^9$-neopentyl-8-(2-(5-phosphono)-furanyl)adenine with 2-(methoxycarbonyloxymethyl)-1,3-propanediol which was prepared as follows:

At page 85, the paragraph that begins at line 9 was replaced with the following paragraph with the noted changes:

A mixture of $N^9$-neopentyl-8-(2-(5-phosphono)furanyl)adenine (1 mmol) and tris(hydroxymethyl)aminomethane (1.05 mmol) in methanol is stirred at 25 °C for 24 h. Evaporation [give] gives $N^9$-neopentyl-8-(2-(5-phosphono)furanyl)adenine tris(hydroxymethyl)aminomethane salt.

At page 85, the paragraph that begins at line 13 was replaced with the following paragraph with the noted changes:

Examples of the methods of the present invention [includes] include the following. It will be understood that these examples are exemplary and that the method of the invention is not limited solely to these examples.

At page 85, the paragraph that begins at line 21 was replaced with the following paragraph with the noted changes:

i. Animals with pancreatic b-cells destroyed by specific chemical cytotoxins such as Alloxan or Streptozotocin (e.g. the Streptozotocin-treated mouse, -rat, dog, and -monkey). Kodama, H., Fujita, M., Yamaguchi, I., [*Japanese] Japanese Journal of Pharmacology* **1994**, *66*, 331-336 (mouse); Youn, J.H., Kim, J.K., Buchanan, T.A., *Diabetes* **1994**, *43*, 564-571 (rat); Le Marchand, Y., Loten, E.G., Assimacopoulos-Jannet, F., et al., *Diabetes* **1978**, *27*, 1182-88 (dog); and Pitkin, R.M., Reynolds, W.A., *Diabetes* **1970**, *19*, 70-85 (monkey).

At page 91, the paragraph beginning on line 24 was replaced with the following paragraph with the noted changes:

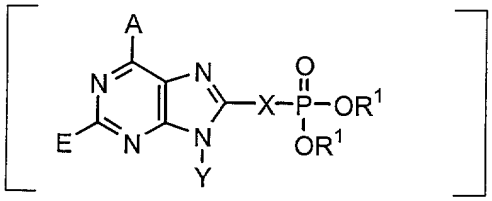
*Phosphofructokinase*: Enzyme (rabbit liver) was purchased from Sigma. Activity was measured at 30 °C in reactions in which the formation of fructose 1,6-bisphosphate was coupled to the oxidation of NADH via the action of aldolase, triosephosphate isomerase, and α-glycerophosphate dehydrogenase. Reaction mixtures (200 µl) were made up in 96-well microtitre plates and were read at 340 nm in a Molecular Devices Microplate Reader. The mixtures consisted of 200 mM Tris-HCl pH 7.0, 2 mM DTT, 2 mM [MgC12] $MgCl_2$, 0.2 mM NADH, 0.2 mM ATP, 0.5 mM Fructose 6-phosphate, 1 unit aldolase/mL, 3 units/mL triosephosphate isomerase, and 4 units/mL α-glycerophosphate dehydrogenase. Test compound concentrations ranged from 1 to 500 µM. Reactions were started by the addition of 0.0025 units of phosphofructokinase and were monitored for 15 minutes.

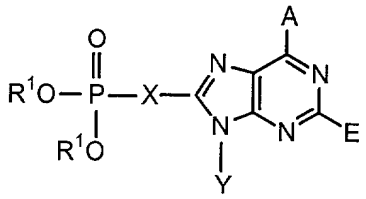
IN THE CLAIMS

Claims 2-33, 40 and 43 were cancelled without prejudice.

Claims 1, 34-37, 39, and 42 were amended as follows with the noted changes:

1. (Amended) A compound of formula 1:





wherein

A is selected from the group consisting of $-NR^8_2$, $-NHSO_2R^3$, $-OR^5$, $-SR^5$, [halogen] halo, lower alkyl, $-CON(R^4)_2$, [guanidine, amidine,] guanidino, amidino, -H, and perhaloalkyl;

E is selected from the group consisting of -H, [halogen] halo, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^7_2$;

X [is selected from the group consisting of alkylamino, alkyl, alkenyl, alkynyl, alkyl(carboxyl), alkyl(hydroxy), alkyl(phosphonate), alkyl(sulfonate), aryl, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alicyclic, 1,1-dihaloalkyl, carbonylalkyl, aminocarbonylamino, alkylaminocarbonyl, alkylcarbonylamino, aralkyl, and alkylaryl, all optionally substituted; or] together with Y forms a cyclic group [including] selected from the group of cyclic alkyl, heterocyclic, and aryl;

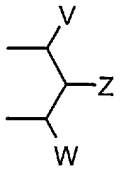
[Y is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-OR^3$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted; or together with X forms a cyclic group including aryl, cyclic alkyl, and heterocyclic;]

$R^1$ is independently selected from the group consisting of -H, alkyl, aryl, [alicyclic] cyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl,



(DOC)

[alkylaryl] –alk-aryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $-C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, [alkyl-S-C(O)$R^3$] –alk-S-C(O)$R^3$, [alkyl-S-S-alkylhydroxy] –alk-S-S-alkylhydroxy, and [alkyl-S-S-S-alkylhydroxy] –alk-S-S-S-alkylhydroxy, or together $R^1$ and $R^1$ are [-alkyl-S-S-alkyl-] –alk-S-S-alk- to form a cyclic group, wherein each "alk" is an independently selected alkylene, or together $R^1$ and $R^1$ are




wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected via a chain of 3-5 atoms, [optionally 1 heteroatom] only one of which can be a heteroatom, to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected via a chain of [to form a cyclic group containing] 3 carbon atoms to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, [and] or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH=CR^2R^2)OH$, $-CH(C\equiv CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

$R^2$ is selected from the group consisting of $R^3$ and -H;

$R^3$ is selected from the group consisting of alkyl, aryl, alicyclic, heteroalicyclic, and aralkyl;

$R^4$ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, and lower aryl;

$R^5$ is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, lower heteroalicyclic, and lower alicyclic;

$R^6$ is independently selected from the group consisting of -H, and lower alkyl;

$R^7$ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

$R^8$ is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together [they] said $R^8$ groups form a bidendate [alkyl] alkylene;

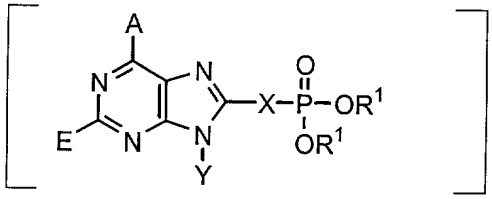
$R^9$ is selected from the group consisting of alkyl, aralkyl, heteroalicyclic, and alicyclic;

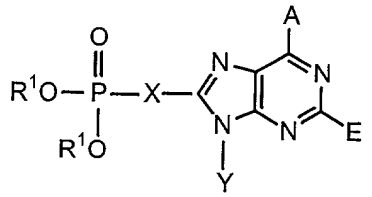
$R^{10}$ is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

$R^{11}$ is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.

34. (Amended) A method of treating an animal for diabetes mellitus, comprising administering to said animal a therapeutically effective amount of a compound of formula (1):





wherein

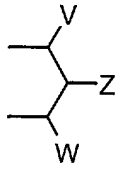
A is selected from the group consisting of $-NR^8{}_2$, $-NHSO_2R^3$, $-OR^5$, $-SR^5$, [halogen] halo, lower alkyl, $-CON(R^4)_2$, [guanidine, amidine,] guanidino, amidino, -H, and perhaloalkyl;

E is selected from the group consisting of -H, [halogen] halo, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^7{}_2$;

X [is selected from the group consisting of alkylamino, alkyl, alkenyl, alkynyl, alkyl(carboxyl), alkyl(hydroxy), alkyl(phosphonate), alkyl(sulfonate), aryl, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alicyclic, 1,1-dihaloalkyl, carbonylalkyl, aminocarbonylamino, alkylaminocarbonyl, alkylcarbonylamino, aralkyl, and alkylaryl, all optionally substituted; or] together with Y forms a cyclic group [including] selected from the group of cyclic alkyl, heterocyclic, and aryl;

[Y is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-OR^3$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted; or together with X forms a cyclic group including aryl, cyclic alkyl, and heterocyclic;]

$R^1$ is independently selected from the group consisting of -H, alkyl, aryl, [alicyclic] heteroalicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, [alkylaryl] –alk-aryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $-C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, [alkyl-S-C(O)$R^3$] –alk-S-C(O)$R^3$, [alkyl-S-S-alkylhydroxy] –alk-S-S-alkylhydroxy, and [alkyl-S-S-S-alkylhydroxy] –alk-S-S-S-alkylhydroxy, or together $R^1$ and $R^1$ are [-alkyl-S-S-alkyl-] –alk-S-S-alk- to form a cyclic group, wherein each "alk" is an independently selected alkylene, or together $R^1$ and $R^1$ are




wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected via a chain of 3-5 atoms, [optionally 1 heteroatom] only one of which can be a heteroatom, to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected via a chain of [to form a cyclic group containing] 3 carbon atoms to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy,

alkylthiocarboxy, hydroxymethyl, [and] or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH=CR^2R^2)OH$, $-CH(C\equiv CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

$R^2$ is selected from the group consisting of $R^3$ and -H;

$R^3$ is selected from the group consisting of alkyl, aryl, alicyclic, heteroalicyclic, and aralkyl;

$R^4$ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, and lower aryl;

$R^5$ is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, lower heteroalicyclic, and lower alicyclic;

$R^6$ is independently selected from the group consisting of -H, and lower alkyl;

$R^7$ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

$R^8$ is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together [they] said $R^8$ groups form a bidendate [alkyl] alkylene;

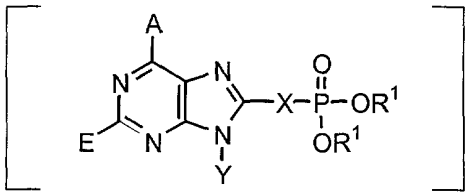
$R^9$ is selected from the group consisting of alkyl, aralkyl, heteroalicyclic, and alicyclic;

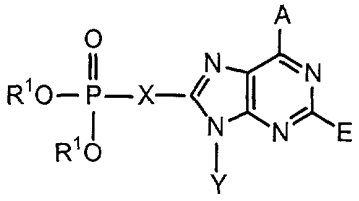
$R^{10}$ is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

$R^{11}$ is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.

35. (Amended) A method of lowering blood glucose levels in an animal in need thereof, comprising administering to said animal a pharmaceutically acceptable amount of a compound of formula (1):





wherein

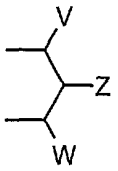
A is selected from the group consisting of $-NR^8_2$, $-NHSO_2R^3$, $-OR^5$, $-SR^5$, [halogen] halo, lower alkyl, $-CON(R^4)_2$, [guanidine, amidine,] guanidino, amidino, -H, and perhaloalkyl;

E is selected from the group consisting of -H, [halogen] halo, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^7_2$;

X [is selected from the group consisting of alkylamino, alkyl, alkenyl, alkynyl, alkyl(carboxyl), alkyl(hydroxy), alkyl(phosphonate), alkyl(sulfonate), aryl, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alicyclic, 1,1-dihaloalkyl, carbonylalkyl, aminocarbonylamino, alkylaminocarbonyl, alkylcarbonylamino, aralkyl, and alkylaryl, all optionally substituted; or] together with Y forms a cyclic group [including] selected from the group of cyclic alkyl, heterocyclic, and aryl;

[Y is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-OR^3$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted; or together with X forms a cyclic group including aryl, cyclic alkyl, and heterocyclic;]

$R^1$ is independently selected from the group consisting of -H, alkyl, aryl, [alicyclic] heteroalicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, [alkylaryl] –alk-aryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $-C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, [alkyl-S-C(O)$R^3$] –alk-S-C(O)$R^3$, [alkyl-S-S-alkylhydroxy] –alk-S-S-alkylhydroxy, and [alkyl-S-S-S-alkylhydroxy] –alk-S-S-S-alkylhydroxy, or together $R^1$ and $R^1$ are [-alkyl-S-S-alkyl-] –alk-S-S-alk- to form a cyclic group, wherein each "alk" is an independently selected alkylene, or together $R^1$ and $R^1$ are




wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and -$R^9$; or

together V and Z are connected via a chain of 3-5 atoms, [optionally 1 heteroatom] only one of which can be a heteroatom, to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected via a chain of [to form a cyclic group containing] 3 carbon atoms to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, [and] or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of -$CH_2OH$, -$CH_2OCOR^3$, -$CH_2OC(O)SR^3$, -$CH_2OCO_2R^3$, -$SR^3$, -$S(O)R^3$, -$CH_2N_3$, -$CH_2NR^2_2$, -$CH_2Ar$, -CH(Ar)OH, -$CH(CH{=}CR^2R^2)OH$, -$CH(C{\equiv}CR^2)OH$, and -$R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is -$R^2$, then at least one of V and W is not -H or -$R^9$;

$R^2$ is selected from the group consisting of $R^3$ and -H;

$R^3$ is selected from the group consisting of alkyl, aryl, alicyclic, heteroalicyclic, and aralkyl;

$R^4$ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, and lower aryl;

$R^5$ is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, lower heteroalicyclic, and lower alicyclic;

$R^6$ is independently selected from the group consisting of -H, and lower alkyl;

$R^7$ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, lower aryl, and -$C(O)R^{10}$;

$R^8$ is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, -C(O)$R^{10}$, or together [they] said $R^8$ groups form a bidendate [alkyl] alkylene;

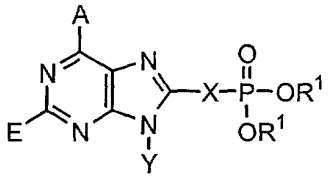
$R^9$ is selected from the group consisting of alkyl, aralkyl, heteroalicyclic, and alicyclic;

$R^{10}$ is selected from the group consisting of -H, lower alkyl, -$NH_2$, lower aryl, and lower perhaloalkyl;

$R^{11}$ is selected from the group consisting of alkyl, aryl, -OH, -$NH_2$ and -$OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.

36. A method of inhibiting FBPase at the AMP site in patients in need thereof, comprising administering to said patients an FBPase inhibitory amount of a compound of formula (1):



wherein

A is selected from the group consisting of -$NR^8{}_2$, -$NHSO_2R^3$, -$OR^5$, -$SR^5$, [halogen] halo, lower alkyl, -$CON(R^4)_2$, [guanidine, amidine,] guanidino, amidino, -H, and perhaloalkyl;

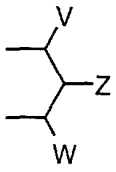
E is selected from the group consisting of -H, [halogen] halo, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and -$NR^7{}_2$;

X [is selected from the group consisting of alkylamino, alkyl, alkenyl, alkynyl, alkyl(carboxyl), alkyl(hydroxy), alkyl(phosphonate), alkyl(sulfonate), aryl, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alicyclic, 1,1-dihaloalkyl, carbonylalkyl, aminocarbonylamino, alkylaminocarbonyl, alkylcarbonylamino, aralkyl, and alkylaryl, all optionally substituted; or] together with Y forms a cyclic group [including] selected from the group of cyclic alkyl, heterocyclic, and aryl;

[Y is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, -C(O)$R^3$, -$S(O)_2R^3$, -C(O)-$OR^3$, -$CONHR^3$, -$NR^2{}_2$, and -$OR^3$,

all except H are optionally substituted; or together with X forms a cyclic group including aryl, cyclic alkyl, and heterocyclic;]

$R^1$ is independently selected from the group consisting of -H, alkyl, aryl, [alicyclic] heteroalicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, [alkylaryl] –alk-aryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2$-OC (O)$R^3$, $-C(R^2)_2$-O-C(O)$OR^3$, $-C(R^2)_2OC(O)SR^3$, [alkyl-S-C(O)$R^3$] –alk-S-C(O)$R^3$, [alkyl-S-S-alkylhydroxy] –alk-S-S-alkylhydroxy, and [alkyl-S-S-S-alkylhydroxy] –alk-S-S-S-alkylhydroxy, or together $R^1$ and $R^1$ are [-alkyl-S-S-alkyl-] –alk-S-S-alk- to form a cyclic group, wherein each "alk" is an independently selected alkylene, or together $R^1$ and $R^1$ are




wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected via a chain of 3-5 atoms, [optionally 1 heteroatom] only one of which can be a heteroatom, to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected via a chain of [to form a cyclic group containing] 3 carbon atoms to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, [and] or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2_2$, $-CH_2Ar$, -CH(Ar)OH, $-CH(CH=CR^2R^2)OH$, $-CH(C\equiv CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

$R^2$ is selected from the group consisting of $R^3$ and -H;

$R^3$ is selected from the group consisting of alkyl, aryl, alicyclic, heteroalicyclic, and aralkyl;

$R^4$ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, and lower aryl;

$R^5$ is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, lower heteroalicyclic, and lower alicyclic;

$R^6$ is independently selected from the group consisting of -H, and lower alkyl;

$R^7$ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

$R^8$ is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together [they] said $R^8$ groups form a bidendate [alkyl] alkylene;

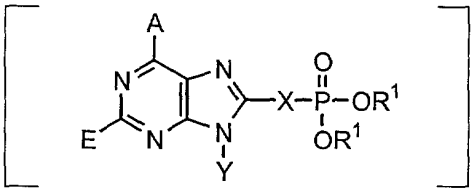
$R^9$ is selected from the group consisting of alkyl, aralkyl, heteroalicyclic, and alicyclic;

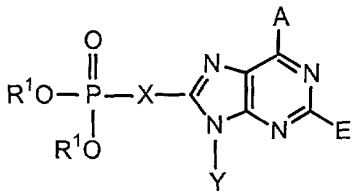
$R^{10}$ is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

$R^{11}$ is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.

37. (Amended) A method of inhibiting gluconeogenesis in animal in need thereof, comprising administering to said animal an effective amount of a compound of formula (1):





wherein

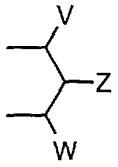
A is selected from the group consisting of $-NR^8_2$, $-NHSO_2R^3$, $-OR^5$, $-SR^5$, [halogen] halo, lower alkyl, $-CON(R^4)_2$, [guanidine, amidine,] guanidino, amidino, -H, and perhaloalkyl;

E is selected from the group consisting of -H, [halogen] halo, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^7_2$;

X [is selected from the group consisting of alkylamino, alkyl, alkenyl, alkynyl, alkyl(carboxyl), alkyl(hydroxy), alkyl(phosphonate), alkyl(sulfonate), aryl, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alicyclic, 1,1-dihaloalkyl, carbonylalkyl, aminocarbonylamino, alkylaminocarbonyl, alkylcarbonylamino, aralkyl, and alkylaryl, all optionally substituted; or] together with Y forms a cyclic group [including] selected from the group of cyclic alkyl, heterocyclic, and aryl;

[Y is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-OR^3$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted; or together with X forms a cyclic group including aryl, cyclic alkyl, and heterocyclic;]

$R^1$ is independently selected from the group consisting of -H, alkyl, aryl, [alicyclic] heteroalicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, [alkylaryl] –alk-aryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $-C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, [alkyl-S-C(O)$R^3$] –alk-S-C(O)$R^3$, [alkyl-S-S-alkylhydroxy] –alk-S-S-alkylhydroxy, and [alkyl-S-S-S-alkylhydroxy] –alk-S-S-S-alkylhydroxy, or together $R^1$ and $R^1$ are [-alkyl-S-S-alkyl-] –alk-S-S-alk- to form a cyclic group, wherein each "alk" is an independently selected alkylene, or together $R^1$ and $R^1$ are




wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected via a chain of 3-5 atoms, [optionally 1 heteroatom] only one of which can be a heteroatom, to form part of a cyclic group substituted with hydroxy,

acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected via a chain of [to form a cyclic group containing] 3 carbon atoms to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, [and] or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH=CR^2R^2)OH$, $-CH(C\equiv CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

$R^2$ is selected from the group consisting of $R^3$ and -H;

$R^3$ is selected from the group consisting of alkyl, aryl, alicyclic, heteroalicyclic, and aralkyl;

$R^4$ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, and lower aryl;

$R^5$ is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, lower heteroalicyclic, and lower alicyclic;

$R^6$ is independently selected from the group consisting of -H, and lower alkyl;

$R^7$ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

$R^8$ is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together [they] said $R^8$ groups form a bidendate [alkyl] alkylene;

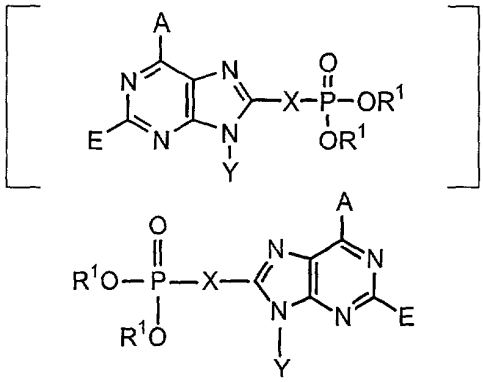
$R^9$ is selected from the group consisting of alkyl, aralkyl, heteroalicyclic, and alicyclic;

$R^{10}$ is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

$R^{11}$ is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.

39. (Amended) A method of treating an animal for a disease derived from abnormally elevated insulin levels, comprising administering to said animal a therapeutically effective amount of a fructose-1,6-bisphosphatase inhibitor wherein said inhibitor is a compound of formula (1):



wherein

A is selected from the group consisting of $-NR^8_2$, $-NHSO_2R^3$, $-OR^5$, $-SR^5$, [halogen] halo, lower alkyl, $-CON(R^4)_2$, [guanidine, amidine,] guanidino, amidino, -H, and perhaloalkyl;

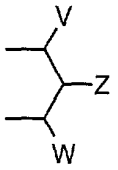
E is selected from the group consisting of -H, [halogen] halo, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^7_2$;

X [is selected from the group consisting of alkylamino, alkyl, alkenyl, alkynyl, alkyl(carboxyl), alkyl(hydroxy), alkyl(phosphonate), alkyl(sulfonate), aryl, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alicyclic, 1,1-dihaloalkyl, carbonylalkyl, aminocarbonylamino, alkylaminocarbonyl, alkylcarbonylamino, aralkyl, and alkylaryl, all optionally substituted; or] together with Y forms a cyclic group [including] selected from the group of cyclic alkyl, heterocyclic, and aryl;

[Y is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-OR^3$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted; or together with X forms a cyclic group including aryl, cyclic alkyl, and heterocyclic;]

$R^1$ is independently selected from the group consisting of -H, alkyl, aryl, [alicyclic] heteroalicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, [alkylaryl] –alk-aryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $-C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, [alkyl-S-C(O)$R^3$] –alk-S-C(O)$R^3$, [alkyl-S-S-alkylhydroxy] –alk-S-S-alkylhydroxy, and [alkyl-S-S-S-alkylhydroxy] –alk-S-S-S-alkylhydroxy, or together $R^1$ and

$R^1$ are [-alkyl-S-S-alkyl-] –alk-S-S-alk- to form a cyclic group, wherein each "alk" is an independently selected alkylene, or together $R^1$ and $R^1$ are




wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected via a chain of 3-5 atoms, [optionally 1 heteroatom] only one of which can be a heteroatom, to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected via a chain of [to form a cyclic group containing] 3 carbon atoms to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, [and] or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH=CR^2R^2)OH$, $-CH(C\equiv CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

$R^2$ is selected from the group consisting of $R^3$ and -H;

$R^3$ is selected from the group consisting of alkyl, aryl, alicyclic, heteroalicyclic, and aralkyl;

$R^4$ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, and lower aryl;

$R^5$ is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, lower heteroalicyclic, and lower alicyclic;

$R^6$ is independently selected from the group consisting of -H, and lower alkyl;

$R^7$ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

$R^8$ is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together [they] said $R^8$ groups form a bidendate [alkyl] alkylene;

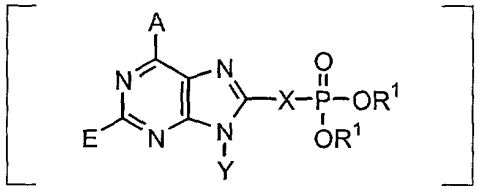
$R^9$ is selected from the group consisting of alkyl, aralkyl, heteroalicyclic, and alicyclic;

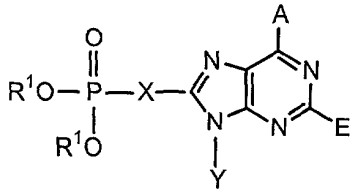
$R^{10}$ is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

$R^{11}$ is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.

42. (Amended) A method of treating an animal with excess glycogen storage disease, comprising administering to said animal in need thereof a therapeutically effective amount of a fructose-1,6-bisphosphatase inhibitor, wherein said inhibitor is a compound of formula (1):





wherein

A is selected from the group consisting of $-NR^8{}_2$, $-NHSO_2R^3$, $-OR^5$, $-SR^5$, [halogen] halo, lower alkyl, $-CON(R^4)_2$, [guanidine, amidine,] guanidino, amidino, -H, and perhaloalkyl;

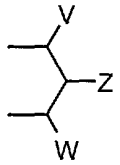
E is selected from the group consisting of -H, [halogen] halo, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^7{}_2$;

X [is selected from the group consisting of alkylamino, alkyl, alkenyl, alkynyl, alkyl(carboxyl), alkyl(hydroxy), alkyl(phosphonate), alkyl(sulfonate), aryl, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alicyclic, 1,1-dihaloalkyl, carbonylalkyl,

aminocarbonylamino, alkylaminocarbonyl, alkylcarbonylamino, aralkyl, and alkylaryl, all optionally substituted; or] together with Y forms a cyclic group [including] selected from the group of cyclic alkyl, heterocyclic, and aryl;

[Y is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-OR^3$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted; or together with X forms a cyclic group including aryl, cyclic alkyl, and heterocyclic;]

$R^1$ is independently selected from the group consisting of -H, alkyl, aryl, [alicyclic] heteroalicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, [alkylaryl] –alk-aryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $-C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, [alkyl-S-C(O)$R^3$] –alk-S-C(O)$R^3$, [alkyl-S-S-alkylhydroxy] –alk-S-S-alkylhydroxy, and [alkyl-S-S-S-alkylhydroxy] –alk-S-S-S-alkylhydroxy, or together $R^1$ and $R^1$ are [-alkyl-S-S-alkyl-] –alk-S-S-alk- to form a cyclic group, wherein each "alk" is an independently selected alkylene, or together $R^1$ and $R^1$ are




wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected via a chain of 3-5 atoms, [optionally 1 heteroatom] only one of which can be a heteroatom, to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected via a chain of [to form a cyclic group containing] 3 carbon atoms to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, [and] or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH=CR^2R^2)OH$, $-CH(C\equiv CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

$R^2$ is selected from the group consisting of $R^3$ and -H;

$R^3$ is selected from the group consisting of alkyl, aryl, alicyclic, heteroalicyclic, and aralkyl;

$R^4$ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, and lower aryl;

$R^5$ is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, lower heteroalicyclic, and lower alicyclic;

$R^6$ is independently selected from the group consisting of -H, and lower alkyl;

$R^7$ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

$R^8$ is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together [they] said $R^8$ groups form a bidendate [alkyl] alkylene;

$R^9$ is selected from the group consisting of alkyl, aralkyl, heteroalicyclic, and alicyclic;

$R^{10}$ is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

$R^{11}$ is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.